Gallbladder Scalloping, Mammillated Caudate Lobe, and Inferior Vena Cava Scalloping: Three Novel Ultrasound Signs of Cirrhosis

Mohammad Amarneh, MD, Ahmed Akhter, MD, M. Zak Rajput, MD, Douglas R. LaBrecque, MD, Monzer Abu-Yousef, MD

Purpose: We aimed to present three new ultrasound signs—gallbladder scalloping, mammillated caudate lobe, and inferior vena cava scalloping—and determine their accuracy in diagnosing liver cirrhosis.

Materials and Methods: A total of 201 consecutive patients with a history of chronic liver disease who had undergone ultrasound imaging and liver biopsy were identified. A senior ultrasound radiologist blindly reviewed the ultrasound examinations. Specificity, sensitivity, positive predictive value, and negative predictive value of diagnosing cirrhosis were calculated for all evaluated ultrasound signs and selected combinations of signs, using the liver biopsy results as the reference standard.

Results: Of the 201 patients, 152 (76%) had either pathology-proven cirrhosis or significant fibrosis. Caudate lobe hypertrophy was the most specific (88%) and most positive predictor (90%) for cirrhosis, whereas mammillated caudate lobe was the most sensitive (78%). Inferior vena cava scalloping was the most specific (78%) of the three proposed ultrasound signs. When signs were combined, the presence of either gallbladder scalloping or liver surface nodularity was highly sensitive for cirrhosis (87%), whereas the presence of either gallbladder scalloping or inferior vena cava scalloping with caudate lobe hypertrophy was highly specific (93%).

Conclusions: Gallbladder scalloping, mammillated caudate lobe, and inferior vena cava scalloping are three novel signs that improve the accuracy of ultrasound in diagnosing cirrhosis.

Key Words: Liver cirrhosis/diagnosis; ultrasonography; sensitivity and specificity.

INTRODUCTION

The diagnosis of cirrhosis using ultrasound (US) is difficult in patients with chronic liver disease. US imaging helps detect liver size and morphology, vascular flow patterns, and the presence or absence of ascites. It is widely accepted that liver surface nodularity and morphological changes such as caudate lobe hypertrophy, when severe enough, can be used to diagnose cirrhosis (1). Despite these findings, and the documented widespread use of US to screen for hepatocellular carcinoma (2), to this day, most physicians still rely on tissue biopsy for diagnosing cirrhosis.

Although perceived to be a definitive test, liver biopsy is not the ideal "gold standard." Needle biopsy obtains a very small piece of tissue—approximately 1/50,000 of the entire liver—and is therefore subject to sampling error; false-negative rates of up to 30% have been reported (3). In addition, despite improvements in technique, biopsy remains an invasive procedure with a risk of complications, including bleeding, infection, and death (4). A need, therefore, exists for a reliable, noninvasive, rapid method for diagnosing liver fibrosis and cirrhosis (5). New techniques, including transient elastography, acoustic radiation force impulse, and magnetic

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The authors declare no conflicts of interest. From the Department of Radiology, University of Iowa Hospitals and Clinics, Iowa City, IA (M.A., M.A.-Y.); Division of Interventional Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA (M.A.); Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin (A.A.); Mallinckrodt Institute of Radiology at Washington University, Saint Louis, MO (M.Z.R.); Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA (D.R.L.). Received December 5, 2017; revised January 30, 2018; accepted February 3, 2018. **Address correspondence to:** M.A. e-mail: dr.amarneh@gmail.com

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resonance elastography have shown promising results. However, cost and operator inexperience have limited their widespread implementation (6,7).

Over the last several years, we have observed a pattern of three unique findings on US examinations of patients with cirrhosis, which we have termed "gallbladder scalloping," "mammillated caudate lobe," and "inferior vena cava (IVC) scalloping." This retrospective study was designed to assess the efficacy of these three signs compared to known sonographic markers in the diagnosis of cirrhosis by correlation with liver pathology.

MATERIALS AND METHODS

Institutional review board approval for this Health Insurance Portability and Accountability Act-compliant retrospective study was obtained for this retrospective study. We identified 201 consecutive patients (73 women and 128 men ranging from 17 to 87 years of age) from our institution between 2006 and 2007 who had a history of chronic liver disease, including, but not limited to, chronic hepatitis C, steatohepatitis, autoimmune hepatitis, primary biliary cirrhosis, and alcoholic liver disease. No patients with acute hepatitis or patients who had undergone imaging outside the institution were included in the study.

Patients underwent diagnostic US following an overnight fast. Examinations were performed by experienced, unblinded ultrasonographers using Acuson Sequoia 512 ultrasound scanners (Siemens Medical Solutions USA Inc., Mountain View, CA) with 8-MHz linear transducers. An established protocol based on the American Institute of Ultrasound in Medicine Practice Guidelines was followed (8). Longitudinal and transverse views of the liver, including both static and real-time images of the left and right lobes of the liver up to the level of the right hemidiaphragm superiorly and right kidney inferiorly, were obtained. The gallbladder was visualized in the longitudinal and transverse planes in both the supine and either of the left decubitus or erect positions. Fluid checks of all four abdominal quadrants were also performed to determine the presence of ascites.

Right intercostal liver biopsy was performed under US guidance using an 18-gauge core needle (10 cm; BioPince, Angiotech Pharmaceuticals Inc., Vancouver, British Columbia). The METAVIR scoring system was used to classify histological grade (0−4) of the biopsy sample (9). For this study, grades 2, 3, and 4 corresponded to moderate fibrosis, severe fibrosis, and established cirrhosis, respectively. Patients in these categories were considered as one group. US findings were compared to the biopsy results, which served as the reference standard for diagnosing cirrhosis.

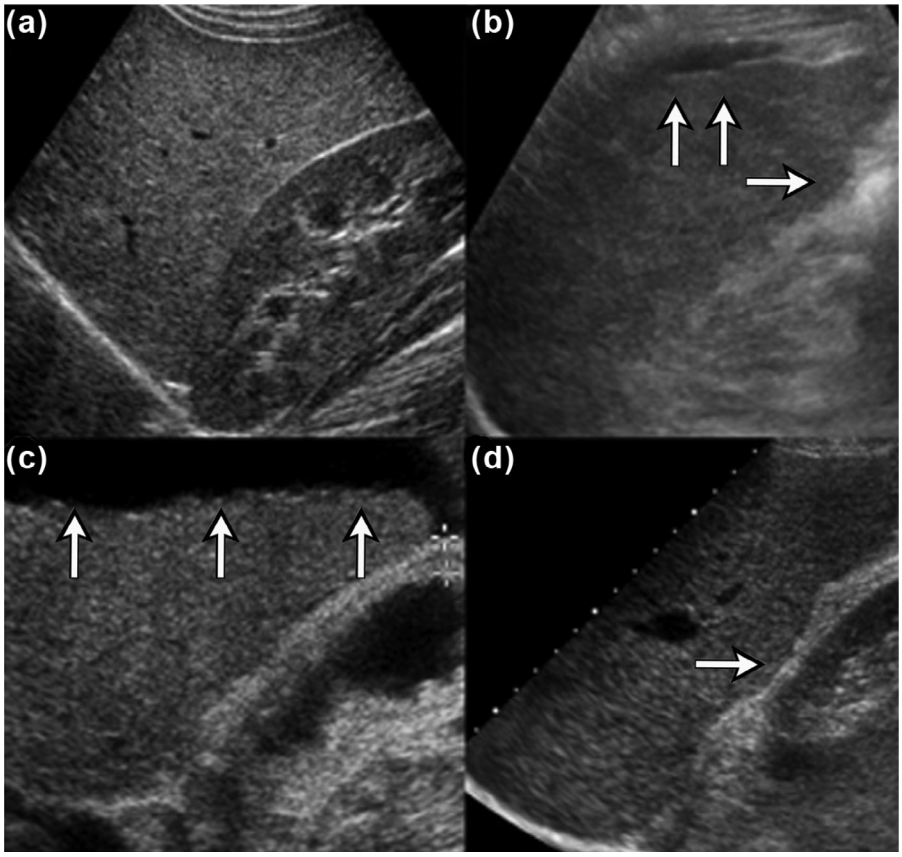

Figure 1. Examples of nodular liver surface: **(a)** normal liver surface; **(b** and **c)** anterior surface nodularity *(arrows)*; and **(d)** posterior surface nodularity along fatty interface *(arrow)*.

The US examinations were reviewed by a specialist (M.A.Y.) with 35 years of experience in abdominal US and 50% clinical time spent in abdominal US who was blinded to the patient's clinical history and final pathological diagnosis. Features qualitatively evaluated on each examination by the specialist included size of the caudate lobe, vascular compression, echotexture (10), liver surface nodularity, and three specific markers: gallbladder scalloping, mammillated caudate lobe, and IVC scalloping (Figs 1–7). The presence of an indentation along the anechoic gallbladder created by nodularity along the inferior surface of the liver denoted gallbladder scalloping. The caudate lobe was considered mammillated when any of its borders lost linear configuration. Scalloping of the IVC occurred when nodularity of the posterior surface of the liver abutted against the anterior surface of the vessel. Findings were classified as either positive (with abnormal features) or negative (normal).

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined for all of the features analyzed on the US examinations. Various US markers were combined to determine if a particular set would result in a higher sensitivity or specificity. A positive sensitivity test was defined by at least one of the markers having to be positive; a positive specificity test was defined as both markers having to be positive (11).

RESULTS

Of the 201 patients, 152 had either pathology-proven cirrhosis or significant fibrosis. Table 1 summarizes the sensitivity, specificity, PPV, and NPV of the known and proposed signs individually. Of all markers, caudate lobe hypertrophy was the most specific (88%) and most positive predictor (90%), whereas mammillated caudate lobe was the most sensitive (78%) and most negative predictor (48%). Both mammillated caudate lobe and gallbladder scalloping had comparable sensitivities to liver surface nodularity and compression of the hepatic veins. Eight of 13 patients with cirrhosis or significant fibrosis negative for any of the known signs were identified on imaging by at least one of the three proposed signs.

US sign combination data are presented in Table 2. With at least one known or proposed sign visualized, sensitivities surpassed those of individual known signs. In addition, when both a known and proposed sign were visualized, specificities rose significantly. Furthermore, in two particular combinations (mammillated caudate lobe and liver surface nodularity, and gallbladder scalloping and mammillated caudate lobe), when observed together, sensitivities (69 and 62%, respectively) were similar to liver surface nodularity, the known sign with the highest sensitivity (74%).

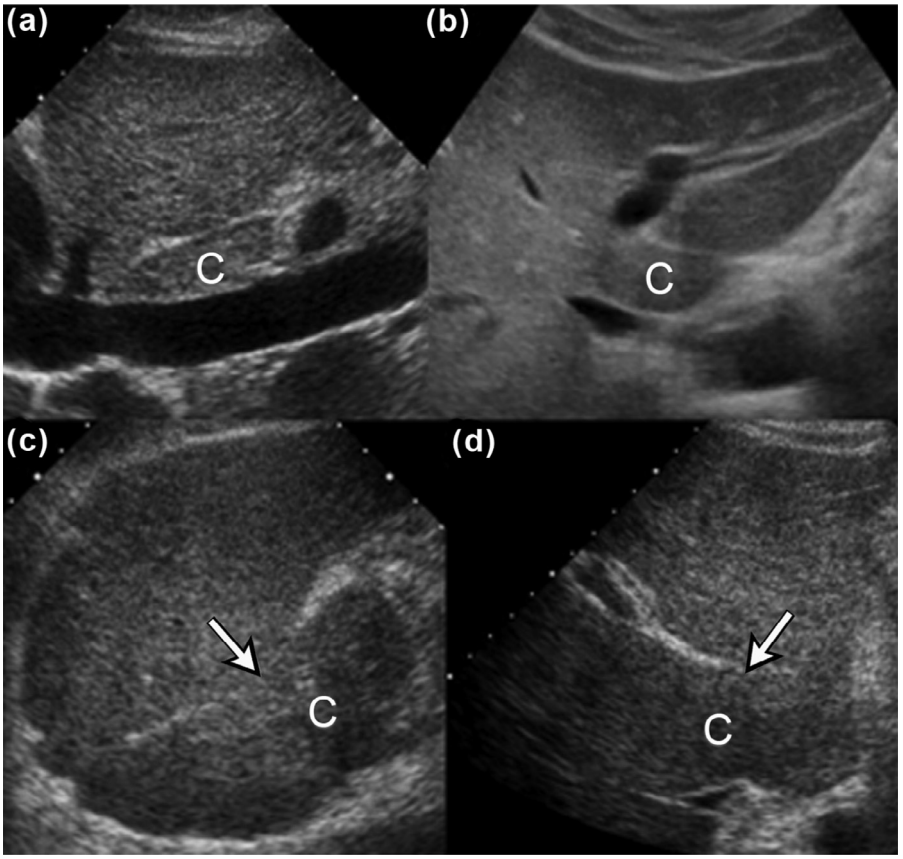

Figure 2. Caudate lobe hypertrophy: (**a** and **b**) longitudinal and transverse views, respectively, of a normal caudate lobe; (**c** and **d**) longitudinal and transverse views, respectively, of a hypertrophied caudate lobe *(arrows demarcating border)*. C, caudate lobe.

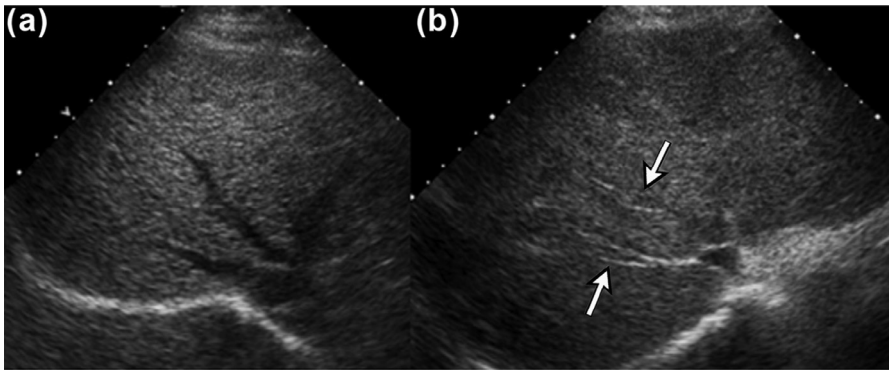

Figure 3. Compressed hepatic veins: **(a)** transverse view of the normal confluence of hepatic veins; **(b)** compressed hepatic veins *(arrows)*.

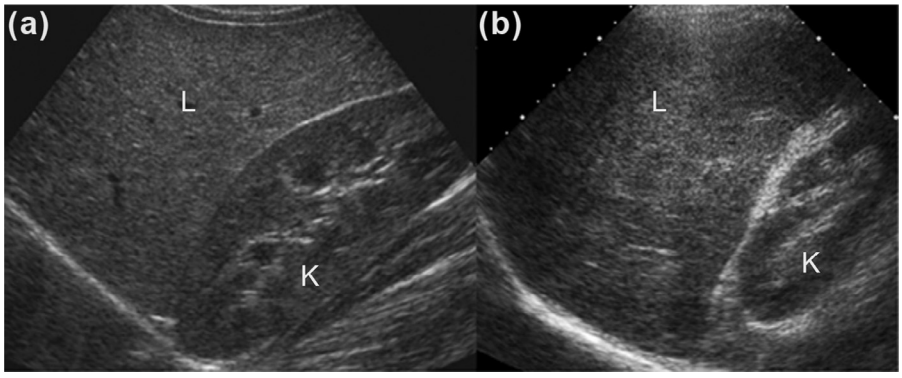

Figure 4. Coarse echotexture: **(a)** normal echogenicity and echotexture; **(b)** coarse echotexture of the liver, although echogenicity is normal. L, liver; K, kidney.

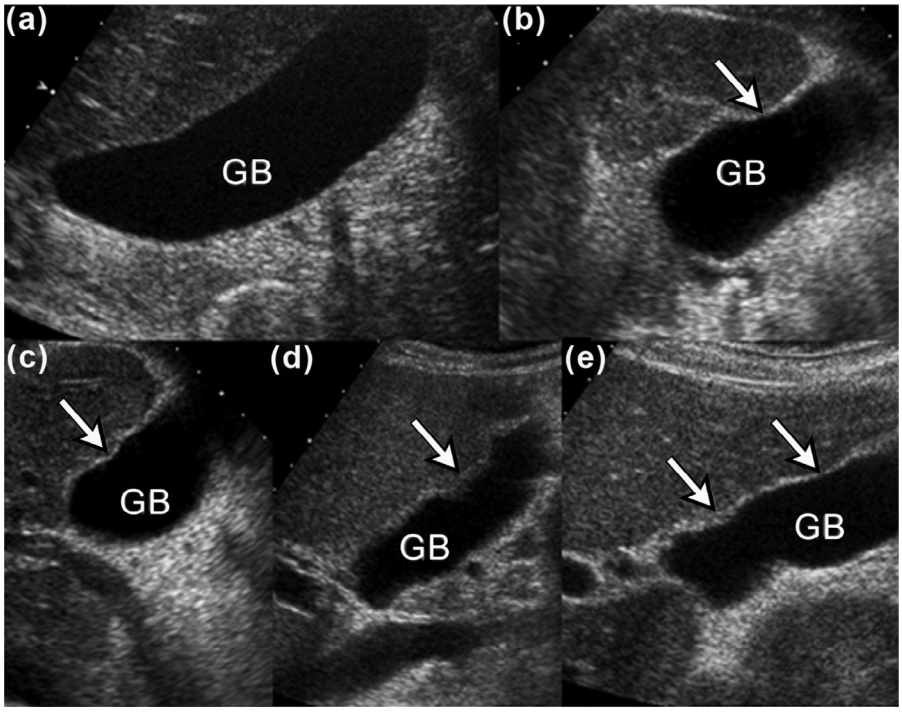

Figure 5. Gallbladder scalloping: **(a)** normal gallbladder; **(b–e)** scalloping of the gallbladder by the nodular liver surface *(arrows)*. GB, gallbladder.

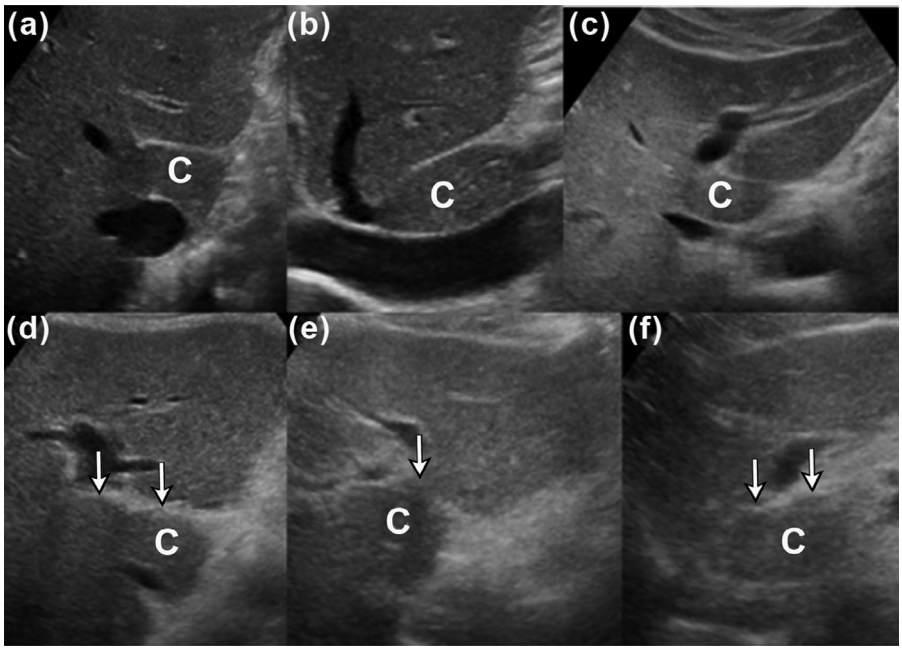

Figure 6. Mammillated caudate lobe: **(a–c)** normal caudate lobe; **(d–f)** beading or nodularity of the caudate lobe surface (arrows). C, caudate lobe.

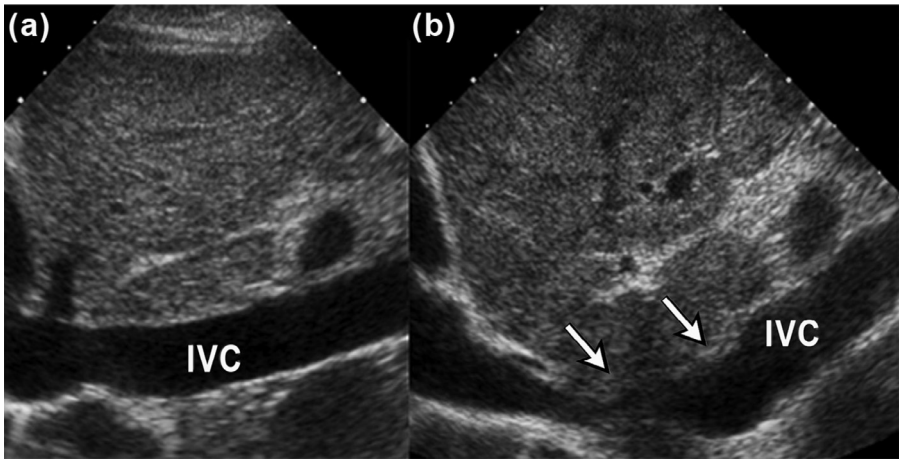

Figure 7. Inferior vena cava scalloping: **(a)** normal inferior vena cava; **(b)** scalloping of the inferior vena cava by the posterior surface of the liver *(arrows)*. IVC, inferior vena cava.

TABLE 1. Diagnostic Performance of Known and Proposed Ultrasound Signs in 201 Patients with Chronic Liver Disease

Ultrasound Sign	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Known				
Caudate lobe hypertrophy	40 (32, 48)	88 (79, 97)	90	33
Hepatic vein compression	67 (60, 74)	72 (59, 85)	88	40
Coarse echotexture	57 (49, 65)	67 (54, 80)	84	34
Liver surface nodularity	74 (67, 81)	61 (47, 75)	85	43
Proposed				
GB scalloping	69 (62, 76)	62 (48, 76)	85	39
Mammillated caudate lobe	78 (71, 85)	60 (46, 74)	85	48
IVC scalloping	46 (38, 54)	78 (66, 90)	87	30

Values in parenthesis are 95% confidence intervals.

GB, gallbladder; IVC, inferior vena cava; NPV, negative predictive value; PPV, positive predictive value.

TABLE 2. Diagnostic Performance of Selected Known and Proposed Ultrasonographic Signs

Ultrasound Sign	Sensitivity (%)	Specificity (%)
At least one present		
GB scalloping and caudate lobe hypertrophy	82 (76, 88)	54 (40, 68)
GB scalloping and liver surface nodularity	87 (82, 92)	47 (33, 61)
GB scalloping and mammillated caudate lobe	86 (80, 92)	39 (25, 53)
Mammillated caudate lobe and caudate lobe hypertrophy	79 (73, 85)	60 (46, 74)
Mammillated caudate lobe and hepatic vein compression	86 (80, 92)	46 (32, 60)
Mammillated caudate lobe and liver surface nodularity	83 (77, 89)	46 (32, 60)
Mammillated caudate lobe and IVC scalloping	82 (76, 88)	55 (41, 69)
IVC scalloping and caudate lobe hypertrophy	64 (56, 72)	73 (61, 85)
Both present		
GB scalloping and caudate lobe hypertrophy	27 (20, 34)	93 (86, 100)
GB scalloping and liver surface nodularity	56 (48, 64)	74 (62, 86)
GB scalloping and mammillated caudate lobe	62 (54, 70)	80 (69, 91)
Mammillated caudate lobe and caudate lobe hypertrophy	39 (31, 47)	88 (79, 97)
Mammillated caudate lobe and hepatic vein compression	56 (48, 64)	89 (80, 98)
Mammillated caudate lobe and liver surface nodularity	69 (62, 76)	77 (65, 89)
Mammillated caudate lobe and IVC scalloping	42 (34, 50)	85 (75, 95)
IVC scalloping and caudate lobe hypertrophy	22 (15, 29)	93 (86, 100)

Values in parenthesis are 95% confidence intervals.
IVC, inferior vena cava; GB, gallbladder.

DISCUSSION

The addition of three ultrasonographic signs—gallbladder scalloping, mammillated caudate lobe, and IVC scalloping—improved the accuracy of diagnosing cirrhosis in patients with chronic liver disease. Mammillated caudate lobe was the most sensitive sign when observed alone. The presence of either gallbladder scalloping or liver surface nodularity yielded a high sensitivity, whereas finding either gallbladder scalloping or IVC scalloping in the presence of caudate lobe hypertrophy produced a high specificity.

Using biopsy as the reference standard, most US markers have high PPV and specificity, but low sensitivity and NPV. Although we did not find the sensitivity and PPV of individual signs to be higher than 88% and 90%, respectively, when markers were combined and used to predict the appearance of cirrhosis, the usefulness of the tests increased dramatically. As expected, with at least one sign present, sensitivities of known and proposed sign combinations became high, surpassing those of known signs when observed alone. With both a known and proposed sign present on examination, specificities were maximized.

Differential size changes of the hepatic lobes, particularly enlargement of the caudate lobe, have been well describedas a marker of cirrhosis (3,12). Harbin et al. achieved a sensitivity of 84% and a specificity of 100% by using the ratio of the transverse width of the caudate lobe to the transverse width of the right lobe, with values above 0.65 indicating a positive finding of caudate lobe hypertrophy (12). However, the study was carried out with a much smaller sample size, with healthy patients with no known history of liver disease serving as the comparison group, and without indication of the clinical or pathological degree of cirrhosis. In addition, both computed tomography and US were used to evaluate caudate lobe morphology and calculate a single set of sensitivity and specificity values (12). Although we did not use a ratio measurement to classify caudate lobe hypertrophy, the sensitivity, specificity, and PPV we obtained are consistent with those observed in other studies in which the only imaging modality employed was US to a sample size similar to ours, where only patients with known chronic liver disease before enrollment were studied (13,14). As a result, it is not unreasonable that the sensitivity for two of our proposed signs—mammillated caudate lobe and gallbladder scalloping—was higher than that of caudate lobe hypertrophy.

Caudate lobe hypertrophy should be distinguished from mammillation of the caudate lobe, as we discovered them to be two distinct findings on US examination. The mechanism of caudate lobe hypertrophy is understood to be related to fibrosis-induced stenosis of the intrahepatic portions of the portal vein and hepatic artery, with relative sparing of the branches supplying the caudate lobe (12). This leads to a greater blood supply to the caudate lobe relative to other portions of the liver, manifesting itself in the observed hypertrophic changes (12). We found caudate lobe hypertrophy to be a less sensitive, but more specific, sign than mammillation in diagnosing cirrhosis. Mammillation, which we believe reflects the presence of regenerative nodules within the caudate lobe parenchyma, may represent a feature more recognizable in the earlier stages of cirrhosis than hypertrophy, which follows secondary changes to the surrounding vasculature.

Historically, the presence of liver surface nodularity on US has been the most commonly used marker to indicate cirrhosis (1,15). In prior studies, the finding was considered to be positive if, instead of a straight and regular hyperechoic edge, the anterior liver surface appeared as a dotted or irregular line and the

liver parenchyma demonstrated areas of different echogenicity (13). For the purposes of this study, we defined liver surface nodularity to be positive findings along either the anterior or posterior surface, with the latter previously categorized as "deep surface nodularity" (16). Filly et al. found that, while the specificity was lower, the sensitivity for detecting cirrhosis of deep surface nodularity was greater than that of the superficial or anterior liver surface (16). We found our definition of liver surface nodularity to have a sensitivity and specificity for detecting cirrhosis consistent not only with Filly et al. but also with prior studies that had assessed only superficial liver surface nodularity (13,17). Minor differences in these values are likely attributable to the fact that we included both superficial and deep surface findings as one group. The presence of both liver surface nodularity and mammillated caudate lobe was shown to be a moderately sensitive marker, surpassing that of several known signs observed in isolation.

The mechanism of scalloping in cirrhotic patients, observed in both the gallbladder and IVC, has not yet been fully elucidated. We hypothesize that a similar phenomenon is occurring in both settings—compression of a pliable fluid collection adjacent to the liver. Of the three proposed signs, IVC scalloping demonstrated the highest specificity and lowest sensitivity, closely paralleling the findings observed with caudate lobe hypertrophy. The hepatic portion of the IVC is encircled between 60% and 100% of its circumference by the caudate lobe of the liver, and it is reasoned that changes in the vessel lumen cannot occur without corresponding changes to the surrounding liver parenchyma (18). Kitamura and Kobayashi discovered a significant reduction in the mean hepatic IVC diameter of patients with biopsy-proven cirrhosis compared to patients with normal livers (18). As we have depicted, IVC scalloping is readily identifiable and may become useful as a highly specific marker for liver cirrhosis, especially when assessment of the caudate lobe is rendered difficult. Further study would involve reassessing the presence and degree of scalloping during deep inspiration, which has been demonstrated to accentuate the differences between normal and cirrhotic patients (18).

Our study was not without potential limitations. With a retrospective review comes susceptibility to multiple forms of bias, including selection bias. All imaging were reviewed by only one, albeit highly experienced, US specialist. As a result, we were unable to test for inter-reader variability, which may have impacted diagnostic performance, particularly in the clinical assessment of deep liver surface nodularity (16). Moreover, patients with moderate fibrosis were considered in addition to those with severe fibrosis or cirrhosis as one group. This was done in an attempt to reduce the false-negative rate and maximize sensitivity. Future study with a larger population would seek to differentiate the performance of our proposed signs with the degree of fibrosis. Nevertheless, the current study comprises, to the best of our knowledge, the first reported investigation assessing the diagnostic performance of these three unique ultrasonographic markers.

The need for biopsy, particularly in at-risk patients, to confirm or exclude the presence of cirrhosis will continue, even with potentially significant improvements in sonographic diagnostic accuracy. Indeed, determination via tissue sample of the degree of fibrosis has shown to be an important negative prognosticator in patients with chronic liver disease (19,20). Nonetheless, noninvasive tests, such as US imaging, can be highly valuable if particular markers on examination are predictive of cirrhosis.

CONCLUSION

Gallbladder scalloping, mammillated caudate lobe, and IVC scalloping are three novel signs that improve the sonographic diagnostic accuracy in diagnosing cirrhosis.

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